

## Supplemental Material – Telomeres

Telomeres are long nucleotide repeats (TTAGGG)<sub>n</sub> and a protein complex at chromosome ends that are essential to chromosomal integrity. All individuals with a telomere biology disorder have abnormally short telomeres for their age, as determined by automated multicolor flow cytometry fluorescence in situ hybridization (flow-FISH) on white blood cell (WBC) subsets. Telomere length testing for DC and related telomere biology disorders is available from a [CLIA-certified laboratory](#).

Telomere length in total leukocytes and in leukocyte subsets (granulocytes, total lymphocytes, naïve T-cells, memory T-cells, B-cells, and natural killer [NK] cells) was determined by flow-FISH on cells from persons with DC, their relatives, and persons with other inherited bone marrow failure syndromes (IBMFS). Data from 400 healthy controls (newborn through age 100 years) was used to generate percentiles of normal telomere length; values below the first percentile for age were considered “very short.”

The diagnostic sensitivity and specificity of very short telomeres was more than 90% in total lymphocytes, naïve T-cells, and B-cells for the diagnosis of DC in comparison with healthy relatives of persons with DC or persons with non-DC IBMFS. Rare healthy relatives with very short telomeres were later shown to have pathogenic variants in the same DC-related gene as the proband. Evaluation of the panel of six leukocyte subsets provided the greatest degree of sensitivity and specificity; the best statistical performance characteristics were obtained by finding very short telomeres in at least three or four of the subsets; granulocytes were the least specific cell type [Alter et al 2007]. A follow-up study with a much larger sample size confirmed this finding [Alter et al 2012]. It also suggested that if the clinical suspicion of DC is high, total lymphocyte telomere length is sufficient for diagnosis. The positive predictive value was 85% in individuals with telomere length below the first percentile for age and a clinical suspicion of DC. However, in less straightforward cases, the six-panel test may be more sensitive and specific.

Note: Another study [Du et al 2009] performed in a different research laboratory using a different technique suggested that peripheral blood mononuclear cell telomere length was less specific for the diagnosis of classic DC; however, the significant differences between the laboratories and analytic methods used suggest that these studies are not directly comparable.

## References

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